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Evaluation of Radiotherapy Planning for Nasopharyngeal Cancer with gEUD Objective and Normal Tissue Objective in Anisotropic Analytical Algorithms and Acuros XB Calculation Models

A. Ghaasyiyah[1,2], A. Azzi[1], A. M.Y. Putranto[3], M. Ambalinggi[3], D. N. Y. Prasada[4], D. S. K. Sihono[1*]

[1]*Department of Physics, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, Depok, 16424, Indonesia*
[2]*Department of Radiation Oncology, Siloam Hospital TB Simatupang, Jakarta, 12430, Indonesia*
[3]*Department of Radiation Oncology, Mochtar Riady Comprehensive Cancer Center, Jakarta, 12930, Indonesia*
[4]*Department of Physics, Faculty of Mathematics and Natural Sciences, Universitas Udayana, Bali, 80361, Indonesia*

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ABSTRACT

This study compared the use of physical (Dose Volume, DV) objectives alone and in combination with biological (generalized Equivalent Uniform Dose, gEUD) objectives, along with various NTO settings, to improve the quality of treatment planning. Ten Nasopharyngeal Cancer (NPC) cases treated with VMAT were selected in this study. The original plans that met standard constraints, were generated using DV objectives and automatic NTO. Two additional plan types were created: (i) DV plans combined with a single upper gEUD for spinal cord, brainstem, and parotids; (ii) DV and DV+gEUD plans with manual Normal Tissue Objective (NTO). Dose calculations were performed using Anisotropic Analytical Algorithm (AAA) and Acuros XB Dose-to-medium (AXB_{Dm}) algorithm. Plans were evaluated for dosimetry, Monitor Unit (MU), and optimization time, with optimal plans were assessed by using Gamma Passing Rate (GPR). Differences between datasets were analyzed using paired t-test. The gEUD objective with $\alpha = 20$ reduced D_{max} by 10% for spinal cord and by 1.21% for brainstem, while D_{mean} to parotids decreased by 25-26% for $\alpha = 10$. However, when $\alpha = 10$ was applied to parotids in combination with $\alpha = 20$ for the spinal cord and brainstem, an increase in D_{max} for the spinal cord and brainstem was observed. The combination of DV and gEUD objectives improved OAR sparing without compromising PTV coverage, with faster optimization and a modest increase in MU. Manual NTO dose fall-off of 0.5 have enhanced conformity and dose fall-off but slightly reduced uniformity in both DV and DV+gEUD plans. The AXB_{Dm} algorithm produced significantly higher gamma passing rates, up to 5% compared to AAA, without in creasing plan complexity. The integration of DV and gEUD objectives improves OAR sparing without compromising PTV coverage or plan quality when appropriate optimization strategies are applied. The selection of NTO settings plays an important role in balancing target dose uniformity and OAR protection. In addition, differences between dose calculation algorithms highlight the importance of algorithm selection, particularly in anatomically heterogeneous regions. Together, careful optimization strategy and algorithm selection contribute to more accurate and clinically robust VMAT planning for NPC cases.

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INTRODUCTION

Nasopharyngeal Cancer (NPC) is predominantly managed with radiotherapy. Given that radiotherapy is the primary modality, achieving optimal treatment planning is essential to ensure adequate target coverage while sparing organs at risk [1]. The complex anatomical position of NPC, adjacent to multiple organs at risk, demands the use of sophisticated radiotherapy techniques to provide sufficient target coverage while effectively

*Corresponding author.
E-mail address: dwi.seno@sci.ui.ac.id
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sparing adjacent organs at risk. Furthermore, the heterogeneous nature of human tissues, including variations in density, emphasizes the need for dose calculation algorithms that provide accurate modeling in inhomogeneous regions. These considerations reinforce the importance of evaluating optimization strategies and calculation models to improve plan quality for NPC [2,3].

In general, inverse treatment planning uses physical dose or Dose-Volume (DV) objectives for dose optimization, and acceptable plans can be achieved in most clinical cases. However, there are limitations in the DV objective that require multiple objectives and will have no available solutions beyond what is already set, and cannot truly reflect the radiation response of the tissues [4]. The generalized Equivalent Uniform Dose (gEUD) objective reflects the biological response to dose distribution. It uses a single organ-specific parameter, namely α values, which describes the volume effect of an organ. Lower α values correspond to parallel organs, where the mean dose is more influential, while higher α values correspond to serial organs, where the maximum dose is more critical [5]. The gEUD objective has improved dose distribution beyond the input parameter since it was found that it is the best dose distribution to other structures [6]. However, achieving optimal results with gEUD objectives can be time-consuming. To overcome the disadvantages of both objectives, several studies that combine DV and gEUD objectives for different cohorts have been conducted. All results demonstrated that the combination of these objectives spared organs at risk (OARs) while maintaining conformity and uniformity of the Planning Target Volume (PTV) [4-7]. However, their optimal results involved the use of different α values for each OAR.

Eclipse Treatment Planning System (TPS) provides additional tools to sculpt dose distribution, namely Normal Tissue Objectives (NTO). NTO is a tool to minimize dose spillage to OARs surrounding a PTV. There are two types of settings for NTO, automatic NTO, which is a vendor-defined automatic formula, and manual NTO. The manual NTO consists of four parameters: margin Xstart, initial dose fo, final dose f∞, and dose fall-off k [8]. Several studies on NTO have been conducted in several clinical cases employing different techniques. In the case of prostate VMAT (Volumetric Modulated Arc Therapy), there was no significant difference between plans with or without NTO, but in the endometrial IMRT case, a significant difference was observed [9,10]. The latest study in brain IMRT (Intensity Modulated Radiation Therapy) cases showed that there were significant differences between plans with or without NTO and showed that manual NTO settings with a dose fall-off of 0.5 and a priority of 100 provided optimal results. Meanwhile, a study on NTO in lung SBRT (Stereotactic Body Radiotherapy) cases reported optimal results when manual NTO settings were used with a dose fall-off of 0.15 and a priority of 500 [11].

In addition to optimization parameters for managing radiation beams, dose calculation is also an important part of treatment planning. The accuracy of dose calculation is essential to ensure that the dose delivered to the tumor corresponds to the prescribed dose. Verification and comparison of dose calculation algorithms are important aspects of treatment planning, as different algorithms may produce differences in the calculated dose distribution (Liura and Pawiro, (2020)) [12]. Usually, TPS uses a model-based algorithm with different approaches. For instance, the Anisotropic Analytical Algorithm (AAA) uses the superposition convolution technique, and the Acuros XB algorithm uses the Linear Boltzmann Transport Equation (LBTE) that considers the material properties of each anatomical region tissue. Acuros XB offers two types of reports for final dose calculation, namely Dose-to-Medium (Dm), which uses a medium-based fluence-to-dose response function, and Dose-to-Water (Dw), which uses a water-based response function. However, Dw conversion involves some uncertainty, so it makes Dm might be preferable for treatment plans. Many studies have compared AAA and AXB in Nasopharyngeal Carcinoma (NPC) cases [2,13]. Based on these studies, AXB provides more accurate results than AAA, especially in heterogeneous media, and predicts a significant dose reduction in bony structures. However, the magnitude of dose reduction in bony structures may affect the homogeneity predicted by AXB.

This study is motivated by the need to improve DV and gEUD objectives for different optimal α values of gEUD in OARs, as well as by the lack of studies on NTO settings for NPC cases. The aim of this study is to evaluate dosimetry and dose verification for planning with DV and gEUD objectives in multiple OARs, with varying α values, and the application of NTO parameters for NPC treated with VMAT. All plans will be calculated using AAA and AXB dose-to-medium (AXB_{Dm}) algorithms to assess their effects on dose accuracy in NPC cases under the optimization parameters studied.

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METHODS

Selection and generation of the treatment plans

Ten NPC patients treated with the VMAT technique were selected for this study. The original plans consisted of three PTVs with prescription doses of 70 Gy, 59.4 Gy, and 54 Gy delivered in 33 fractions, and several OARs were also delineated. All patients were treated using a Varian Clinac iX machine equipped with a Millennium 120 Multi-Leaf Collimator (MLC). All treatment plans were generated in the Eclipse TPS v13.6 using two full arcs and a 6 MV photon beam. The optimization parameters employed DV objectives with priorities based on the desired planning goals, and the NTO was set to automatic with a priority value of 100. Dose calculation was performed using the AAA algorithm with a 2.5 mm grid resolution. Dose constraints for the spinal cord, brainstem, and parotids were based on institutional protocols derived from QUANTEC guidelines. These plans are referred to as DV plans.

In addition, the study was conducted by copying the DV plans to modify the algorithm of optimization and dose calculation while maintaining the same grid resolution. A schematic diagram of the planning design is shown in Fig. 1 and summarized in Tables 1 and 2. In total, 10 DV plans, 60 DV+gEUD plans, 140 manual NTO plans, and 210 plans recalculated using AXB_{Dm} were generated.

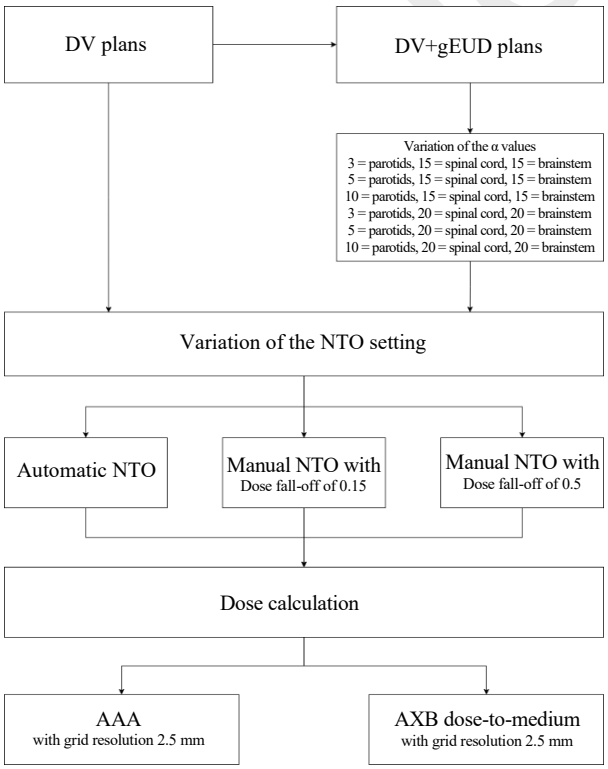


Fig. 1. Planning design for ten NPC cases.

Table 1. Planning objectives and constraints.

OARs	DV Plans	DV+gEUD Plans
Parotids	Mean ≤ 22 Gy Priority 65	Mean ≤ 22 Gy, priority 65 Upper gEUD = 90% of DV dose constraint α = 3, 5, 10 priority 75
Spinal cord	Max ≤ 33 Gy Priority 65	Max ≤ 33 Gy, priority 65 Upper gEUD = 90% of DV dose constraint α = 15, 20 priority 75
Brainstem	Max ≤ 44 Gy Priority 65	Max ≤ 44 Gy, priority 65 Upper gEUD = 90% of DV dose constraint α = 15, 20 priority 75

Table 2. NTO settings in DV and DV+gEUD plans.

NTO settings	Values
Automatic NTO	
Priority	100
Manual NTO	
x-start	1 mm
fo	105%
f∞	60%
Dose fall-off	0.15 and 0.5
Priority	100

Evaluation and analysis

Each plan was evaluated using the dose volume histogram (DVH) and various comparison indices. The DVH parameters followed ICRU report No. 83, while dose limits for OARs were based on the QUANTEC guidelines. For PTVs, the D98%, D95%, D50%, and D2% were compared. The maximum dose (D_{max}) was used for serial OARs (brainstem, spinal cord, optic nerve, optic chiasm, lens, and mandible), whereas the mean dose (D_{mean}) was used for parallel OARs (parotids, larynx, oral cavity, and trachea) in the comparison [14,15]. Additionally, differences in Monitor Units (MUs) and optimization time were evaluated. For dose evaluation, the Conformity Index (CI) was used to represent PTV dose coverage, the Homogeneity Index (HI) to represent PTV dose uniformity, the Gradient Index (GI) and the Modified Gradient Index (mGi) to represent dose fall-off steepness outside PTV. The CI was calculated using Van't Riet and Paddick's formula as described in Eq. (1). The ideal value of CI is 1, where TVRI denotes the target volume covered by the reference isodose (95% of the prescribed dose) [16].

$$CI = \frac{TV_{RI}}{TV} X \frac{TV_{RI}}{V_{RI}} \quad (1)$$

Homogeneity Index (HI) measures dose uniformity within the PTV. Ideal value of HI is 0, calculated following Eq. (2) [8].

$$HI = \frac{D_{2\%} - D_{98\%}}{D_p} \quad (2)$$

The Gradient Index (GI) assesses dose fall-off steepness outside PTV. A lower GI indicates better healthy tissue sparing, calculated following Eq. (3) [17]:

$$GI = \frac{V_{50\%}}{V_{100\%}} \quad (3)$$

Modified Gradient Index (mGI) is a modified version of GI that considers dose conformity to the PTV. A lower mGI indicates a steeper dose reduction, calculated following Eq. (4) [8]:

$$mGI = \frac{V_{50\%}}{TV} = \frac{V_{50\%}}{V_{100\%}} X \frac{V_{RI}}{TV} \quad (4)$$

To evaluate the effect of optimization parameters and the two dose calculation algorithms on the treatment plans, we performed PSQA for the ten patients with the Perpendicular Field-by-Field (PFF) method, following AAPM Task Group 218 guidelines. Measurements were conducted using an aS1000 EPID mounted on a Varian Clinac iX. PSQA results were assessed using the gamma index. The evaluation parameters were Dose Difference (DD) and Distance to Agreement (DTA) of 3%/2mm, with 10% threshold to exclude low-dose areas that could falsely improve the Gamma Passing Rate (GPR) [18]. The 3%/3mm gamma criterion was also calculated, as it is commonly used in clinical practice. Additionally, statistical analysis was performed using paired t-tests to evaluate the mean differences between two related datasets. A two-tailed p-value of < 0.05 was considered statistically significant.

RESULTS

DV and DV+gEUD plans

Based on DVH and evaluation indices (as shown in Figs. 2-3 and Tables 3-5), the addition of gEUD objectives to multiple OARs resulted in greater reductions in D_{max} and D_{mean} compared with DV plans, while maintaining comparable PTV conformity and homogeneity. The largest D_{max} reduction was observed in DV+gEUD plans with α values of 3 and 20, as well as 5 and 20, showing decreases of up to 10% for the spinal cord and 1.21% for the brainstem. The largest D_{mean} reduction occurred in DV+gEUD with α values of 10 and 15 as well as 10 and 20, with reductions of around 25-26%, and statistically significant differences were observed for spinal cord ($\alpha = 20$) and parotids ($p < 0.05$).

The Indices (CI, HI, GI, and mGI) and PTV results indicated that DV+gEUD plans with α values of 3 and 20, as well as 5 and 20, approached ideal values, with statistically significant differences found in HI, CI, D98%, and D2% for PTV 70 Gy, and D95% for PTV 59.4 Gy. The highest Mus were found in DV+gEUD plans with α values of 10 and 15, as well as 10 and 20, which were around 7-9% higher than DV plans, although these differences were not statistically significant. DV+gEUD plans were optimized significantly faster than DV plans, with time savings of 11-14% (approximately 55-72 seconds).

NTO settings in DV and DV+gEUD plans

Based on DVH and evaluation indices (as shown in Figs. 2-3 and Tables 3-5), the differences between automatic and manual NTO for the CI were below 0.02, for the HIs were approximately 0.01, for the GIs were below 0.04, and for the mGIs were below 0.06, with the largest differences observed in DV plans. For PTV 70 Gy, manual NTO yielded lower D98% and D95% than automatic NTO, with differences of less than 0.39%, whereas D2% and D50% were higher by up to 0.88%. Similar trends were observed for PTV 59.4 Gy and 54 Gy, with differences of less than 1.51%.

For OARs with gEUD, manual NTO with a dose fall-off of 0.5 achieved the lowest doses, with reductions of ~1.52% in the brainstem and ~3% in the spinal cord. However, it slightly increased the mean dose to parotids by up to ~3%. Similar results were observed in OARs without gEUD, with the largest dose differences reaching up to 12%. Statistically, manual NTO with a dose fall-off of 0.5 showed the most significant improvements across both DV and DV+gEUD plans. The average MUs were highest for manual NTO with a dose fall-off of 0.5, showing increases of 0.17-2.18% compared with other NTO settings, although these differences were not statistically significant. In contrast, manual NTO, a dose fall-off of 0.5 resulted in the fastest optimization times among other NTO settings, with a significant reduction of around 7-20%.

Planning with AAA and AXB_{Dm} algorithms

Based on the DVH analysis and evaluation indices (as shown in Figs. 2-3 and Tables 3-5), AXB_{Dm} generally underestimated doses compared to the AAA. For the PTV 70 Gy in both DV and DV+gEUD plans across all NTO settings, AXB_{Dm} produced lower D98%, D95%, and D50% than AAA, with differences of up to 0.66%, whereas D2% was higher by up to 0.66% in DV and 0.1% in DV+gEUD plans. For the PTV 59.4 Gy, the AXB_{Dm} yielded D95% values that were 1-1.13% lower and D50% that were 0.31-0.37% lower than those from

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AAA. Similar results were shown for PTV 54 Gy, with differences of up to 0.4%. Only D95% for PTV 59.4 Gy showed a significant difference between the two algorithms. Overall, AAA produced slightly better evaluation indices (CI, HI, GI, and mGI), with statistically significant differences observed for HI.

In DV plans with varying NTO settings, AXB_{Dm} produced lower D_{max} values than AAA by 0-2.24% for soft tissue organs like brainstem, spinal cord, optic nerve, and optic chiasm, except for optic nerve and chiasm under automatic NTO, where doses were approximately 1% higher. AXB_{Dm} also reduced D_{max} in the lens by 5-6% and in the mandible by 1.16-1.59%. D_{mean} in soft tissue (parotids) was lower by 1.62-1.9%, while reductions in D_{mean} for the oral cavity and trachea were minimal (0-0.16%). In contrast, the larynx exhibited higher doses with AXB_{Dm}, with an increase of 1.11-1.25%.

In DV+gEUD plans with varying NTO settings, AXB_{Dm} typically produced lower D_{max} (up to 1.8%) and D_{mean} (up to 2.4%) for OARs with gEUD objectives compared to AAA, with the greatest reductions observed at an α value of 20 for D_{max} and 10 for D_{mean}. In contrast, combinations of α values of 10 and 15, as well as 10 and 20, resulted in dose increases, like those with AAA. Overall, AXB_{Dm} showed greater dose reduction for OARs optimized with gEUD objectives than DV-only plans, outperforming AAA. For OARs without gEUD objectives, AXB_{Dm} resulted in lower D_{max} for the optic nerve, optic chiasm, lens, and mandible. AXB_{Dm} produced lower D_{mean} for the trachea but higher for the larynx, while D_{mean} values for the oral cavity varied. The α value combinations of 3 and 20, as well as 5 and 20, provided consistent dose reductions across most OARs, like the AAA results, with manual NTO using a dose fall-off of 0.5 achieving the most effective dose reduction across both algorithms.

AXB_{Dm} consistently yielded higher Mus than AAA, with statistically significant differences. In DV+gEUD plans, the highest MU values were observed for α value combinations of 10 and 15 as well as 10 and 20. For NTO variations, the highest MU occurred with manual NTO using a dose fall-off of 0.5, consistent with the results obtained using AAA.

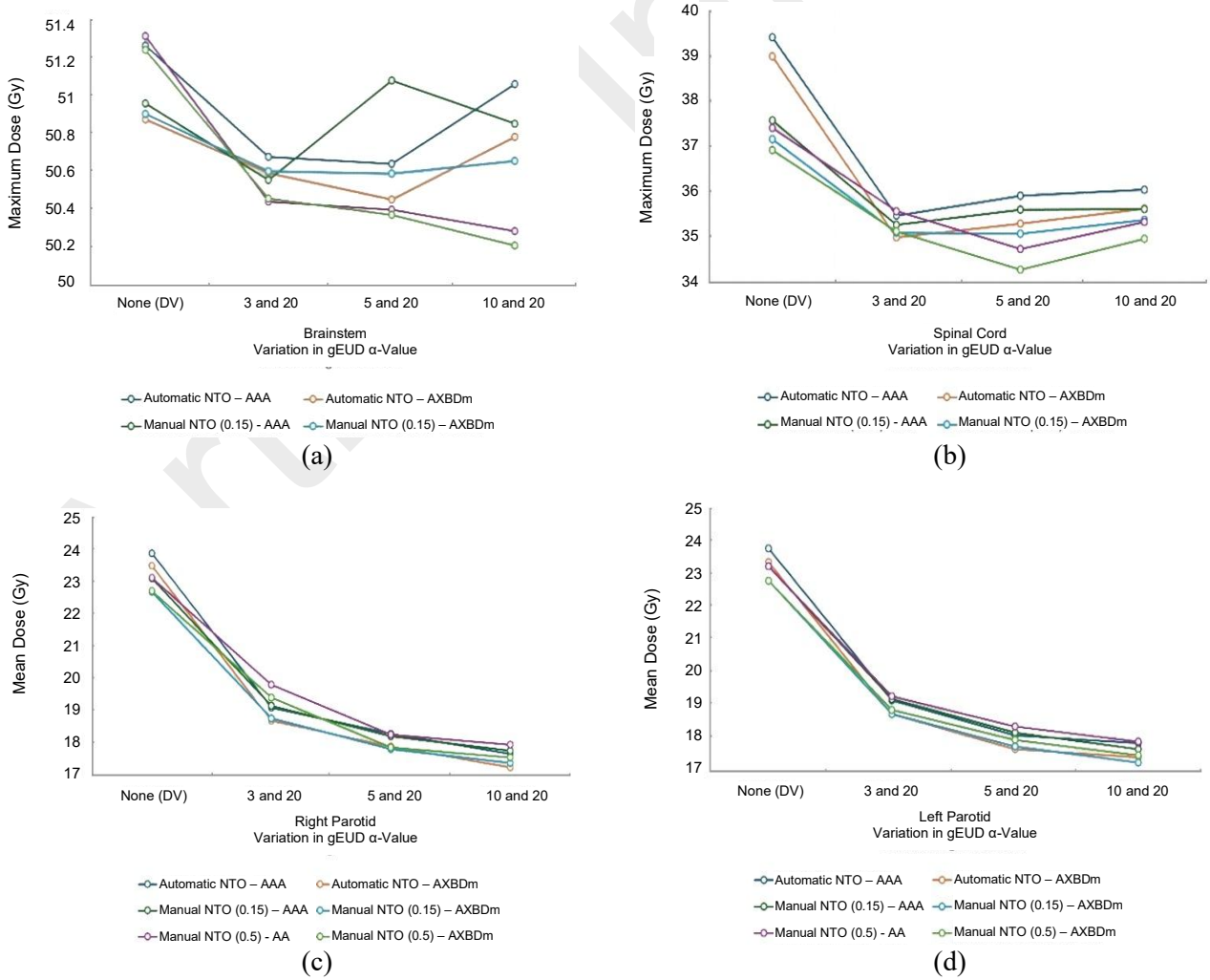


Fig. 2. Average maximum (a,b) and mean (c, d) dose of OARs with gEUD in DV and DV+gEUD with α value of 20.

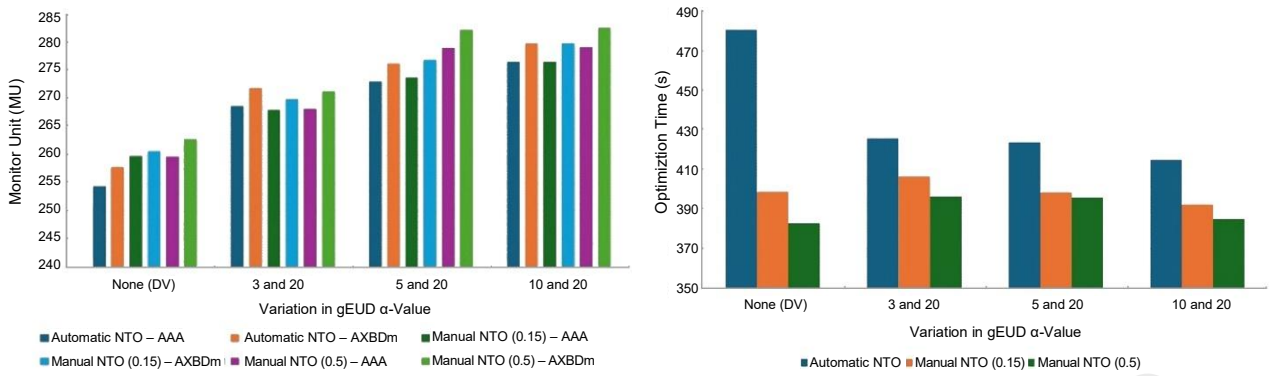


Fig. 3. Average Monitor Unit (MU) (a) and optimization time (b) in DV and DV+gEUD with α value of 20.

Table 3. Average mean dose of OARs without gEUD in DV and DV+gEUD with α value of 20.

OAR without gEUD	Plans	Automatic NTO		Manual NTO with a dose fall-off (0.15)		Manual NTO with a dose fall-off (0.5)	
		AAA	AXB_{Dm}	AAA	AXB_{Dm}	AAA	AXB_{Dm}
		D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)
Oral Cavity	DV	47.8	47.9	46.7	46.7	46.5	46.5
	gEUD 3 and 20	48.6	48.6	48.0	48.2	47.1	47.2
	gEUD 5 and 20	49.1	49.1	47.8	47.8	47.3	47.3
	gEUD 10 and 20	47.9	47.9	47.5	47.5	47.3	47.3
Larynx	DV	21.7	22.0	21.8	22.0	21.8	22.1
	gEUD 3 and 20	21.7	22.0	21.7	22.0	21.8	22.1
	gEUD 5 and 20	21.6	21.9	21.6	21.8	21.6	21.8
	gEUD 10 and 20	21.6	21.9	21.7	22.0	21.7	22.0
Trachea	DV	24.4	24.4	24.1	24.1	23.7	23.7
	gEUD 3 and 20	24.2	24.1	24.0	24.0	23.7	23.7
	gEUD 5 and 20	24.0	24.0	23.9	23.9	23.7	23.6
	gEUD 10 and 20	24.0	24.0	23.7	23.7	23.8	23.8

Table 4. Average maximum dose of OARs without gEUD in DV and DV+gEUD with α value of 20.

OAR without gEUD	Plans	Automatic NTO		Manual NTO with a dose fall-off (0.15)		Manual NTO with a dose fall-off (0.5)	
		AAA	AXB_{Dm}	AAA	AXB_{Dm}	AAA	AXB_{Dm}
		D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)	D_{max} (Gy)
Optic Nerve Right	DV	24.5	24.6	24.3	24.3	22.0	21.9
	gEUD 3 and 20	24.8	24.7	24.7	24.5	23.2	22.8
	gEUD 5 and 20	25.0	25.0	24.1	24	22.3	21.9
	gEUD 10 and 20	24.1	24.1	23.6	23.6	22.0	21.8
Optic Nerve Left	DV	22.8	23.0	23.9	23.8	21.2	21.0
	gEUD 3 and 20	23.9	23.9	23.8	23.6	21.5	21.5
	gEUD 5 and 20	23.6	23.6	23.9	23.8	21.4	21
	gEUD 10 and 20	23.1	23.1	23.2	23.2	20.3	20.3
Optic Chiasm	DV	20.2	20.6	21.9	21.8	20.0	19.5
	gEUD 3 and 20	21.9	21.9	21.6	21.4	20.7	20.4
	gEUD 5 and 20	21.9	21.8	21.4	21.4	19.9	19.7
	gEUD 10 and 20	21.4	21.3	21.6	21.3	19.8	19.4
Lens Right	DV	5.2	4.9	5.1	4.8	5.1	4.8
	gEUD 3 and 20	5.2	4.9	5.2	4.8	5.1	4.8
	gEUD 5 and 20	5.2	4.9	5.2	4.9	5.1	4.8
	gEUD 10 and 20	5.3	5.0	5.3	5.0	5.2	4.9
Lens Left	DV	5.3	5.0	5.1	4.8	5.1	4.8
	gEUD 3 and 20	5.2	4.9	5.2	4.9	5.2	4.9
	gEUD 5 and 20	5.3	5.0	5.2	4.9	5.1	4.8
	gEUD 10 and 20	5.3	5.0	5.2	4.9	5.2	4.9
Mandible	DV	66.0	65.2	66.7	65.6	66.8	65.8
	gEUD 3 and 20	66.9	65.8	66.9	65.8	66.8	65.7
	gEUD 5 and 20	67.1	66.0	66.9	65.9	66.7	65.7
	gEUD 10 and 20	67.1	65.7	67.3	65.9	67.6	66.1

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Table 5. Average values of dosimetry parameters for PTV 70 Gy, 59.4 Gy, and 54 Gy in DV and DV+gEUD with an α value of 20.

PTV	Dosimetry Parameter	Plans	Automatic NTO		Manual NTO with a dose fall-off (0.15)		Manual NTO with a dose fall-off (0.5)	
			AAA	AXB_{Dm}	AAA	AXB_{Dm}	AAA	AXB_{Dm}
			Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)	Dose (Gy)
PTV 70 Gy	D98 %	DV	68.5	68.0	68.3	68.0	68.2	67.9
		gEUD 3 and 20	68.3	67.9	68.2	67.8	68.2	67.8
		gEUD 5 and 20	68.3	67.9	68.2	67.9	68.2	67.8
		gEUD 10 and 20	68.1	67.8	68.2	67.8	68.1	67.7
	D95%	DV	69.1	68.8	69.1	68.9	69.1	68.8
		gEUD 3 and 20	69.1	68.8	69.1	68.8	69.0	68.8
		gEUD 5 and 20	69.1	68.9	69.1	68.8	69.0	68.8
		gEUD 10 and 20	69.0	68.8	69.0	68.8	69.0	68.7
	D50%	DV	71.7	71.5	71.9	71.9	71.9	71.9
		gEUD 3 and 20	71.9	71.9	71.9	71.9	72.0	72
		gEUD 5 and 20	71.9	71.9	72.0	72.0	71.9	72.0
		gEUD 10 and 20	72.0	72.0	71.9	72.0	72	72.0
	D2%	DV	73.3	73.8	73.8	73.8	73.9	73.9
		gEUD 3 and 20	73.9	73.9	73.9	73.9	74.0	74.0
		gEUD 5 and 20	73.9	73.8	74.0	74.0	74.0	74.0
		gEUD 10 and 20	74.1	74.0	74.0	74.0	74.2	74.1
PTV 59.4 Gy	D95%	DV	58.0	57.6	57.5	57.3	57.1	56.5
		gEUD 3 and 20	57.3	56.7	57.1	57.0	56.5	56.0
		gEUD 5 and 20	57.1	56.4	56.9	56.7	56.6	55.9
		gEUD 10 and 20	56.8	56.1	56.5	56.4	56.1	55.4
	D50%	DV	61.6	61.4	61.5	61.4	61.6	61.4
		gEUD 3 and 20	61.6	61.4	61.6	61.4	61.5	61.3
		gEUD 5 and 20	61.5	61.3	61.6	61.4	61.5	61.3
		gEUD 10 and 20	61.6	61.4	61.5	61.3	61.5	61.3
PTV 54 Gy	D95%	DV	53.5	53.4	53.1	53.1	53.2	53.1
		gEUD 3 and 20	53.3	53.2	53.2	53.1	53.1	53.0
		gEUD 5 and 20	53.4	53.3	53.3	53.3	53.2	53.1
		gEUD 10 and 20	53.4	53.4	53.3	53.2	53.1	53.0
	D50%	DV	55.8	55.9	55.9	55.9	56.3	56.0
		gEUD 3 and 20	55.9	55.8	55.9	55.9	56.0	56.0
		gEUD 5 and 20	55.9	55.8	56.0	56.0	56.0	55.9
		gEUD 10 and 20	56.0	55.9	55.9	55.9	56.2	56.0

Gamma index

PSQA (Patient-Specific Quality Assurance) was performed only on plans yielding optimal results with both AAA and AXB_{Dm} algorithms. DVH evaluation shows that the DV+gEUD plans with α value combinations of 3 and 20, as well as 5 and 20, using automatic NTO settings delivered optimal results comparable to clinical DV plans with automatic NTO. Tables 6 and 7 show the mean values, relative differences, and statistical analysis results for gamma index criteria of 3%/2 mm and 3%/3 mm.

For the 3%/2 mm gamma index criterion, the gamma passing rate (GPR) values in DV and DV+gEUD plans were nearly identical, with differences of less than 0.6% for AAA and less than 0.1% for AXB_{Dm}. Comparison of GPR values between AAA and AXB_{Dm} demonstrated that AXB_{Dm} yielded significantly higher GPRs, with differences of less than 6%. For the 3%/3 mm criteria, differences in GPR values between DV and DV+gEUD plans were below 0.2% for both algorithms. However, AXBDm again showed higher GPR values than AAA, with statistically significant differences of approximately 1.9%.

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Table 6. Mean GPR%, relative differences, and statistical analysis for gamma index criteria 3%/2mm/10%threshold.

GPR%	AXB_{Dm}	AAA	AXB_{Dm} - AAA		(DV+gEUD) – DV			
Plans	(mean±SD)	(mean±SD)	(%)	p-value	(%)		p-value	
					AAA	AXB_{Dm}	AAA	AXB_{Dm}
DV	99.3 ± 0.4	94.2 ± 1.6	5.37	0,000				
gEUD 3 and 20	99.2 ± 0.5	93.7 ± 1.8	5.90	0,000	-0.57	-0.07	0.251	0.559
gEUD 5 and 20	99.2 ± 0.3	94.7 ± 1.7	4.76	0,000	0.49	-0.10	0.240	0.367

Table 7. Mean GPR%, relative differences, and statistical analysis for gamma index criteria 3%/3mm.

GPR%	AXB_{Dm}	AAA	AXB_{Dm} - AAA		(DV+gEUD) – DV			
Plans	(mean±SD)	(mean±SD)	(%)	p-value	(%)		p-value	
					AAA	AXB_{Dm}	AAA	AXB_{Dm}
DV	99.8 ± 0.1	98.0 ± 0.8	1.81	0.000				
gEUD 3 and 20	99.6 ± 0.5	97.8 ± 0.7	1.80	0.000	-0.14	-0.15	0.422	0.276
gEUD 5 and 20	99.7 ± 0.2	98.2 ± 0.7	1.55	0.000	0.20	-0.06	0.200	0.170

DISCUSSION

In this study, we evaluated dose distributions using combined DV and gEUD objectives for OARs, with various NTO settings under the AAA and AXB_{Dm} algorithms. The results demonstrated that integrating DV and gEUD objectives for brainstem, spinal cord, and parotids significantly improved OAR sparing without compromising PTV conformity and homogeneity when appropriate α values were selected according to the seriality of the structures. Optimal D_{max} reductions in the spinal cord and brainstem were achieved with an α value of 20, while the D_{mean} to the parotids was most effectively reduced with an α value of 10. However, α value combinations 10 and 20 unexpectedly increased to D_{max} in the spinal cord and brainstem.

The efficacy of gEUD objectives has been shown to correlate with the PTV-OAR distance, as demonstrated in previous studies, which reported an association among the α value, PTV-OAR distance, and the seriality of the structure [19]. In the present study, the proximity between the brainstem and PTV (within 1 cm) limited dose reduction, whereas the spinal cord (located 1.3-2.5 cm from the PVT) and the parotids (structures cropped from the PTV with a separation of 2-3 cm) exhibited more substantial dose sparing. These findings indicate that gEUD is more effective with greater PTV-OAR separation, making the choice of α value dependent on both OAR seriality and proximity to the PTV.

For OARs without gEUD objectives, dose variations were observed due to the whole-structure optimization approach inherent to gEUD. Optimization using gEUD objectives is based on the entire structure rather than on partial volumes of the structure. Therefore, gEUD is less stringent than multiple DV constraints, allowing control of violation of some DV while achieving overall dose goals [20]. Despite this, DV+gEUD plans demonstrated PTV conformity and homogeneity comparable to DV plans, with statistically significant differences observed in CI, HI, D98%, and D2% of PTV 70 Gy and in D95% of PTV 59.4 Gy.

These results demonstrate that the use of combinations of equally large α values (e.g., 10 and 15 as well as 10 and 20) tends to reduce PTV conformity and homogeneity. This effect arises because the large α value, which focuses on reducing high-dose levels within OAR volumes, comes at the expense of uniform dose coverage and conformity to the PTV. The trade-off reflects the fact that sparing high-dose volumes in OARs located close to the target can reduce high-dose coverage within the target area itself, leading to hotspots and incomplete dose coverage of PTV.

In contrast, a combination of small and large α values provides a more balanced optimization strategy. Small α values primarily reduce low and medium dose regions, whereas large α values focus on sparing high-dose volumes in OARs [20]. This complementary approach enables better control of dose distribution to OARs while maintaining adequate dose coverage and a more uniform dose within PTV. By distributing optimization across different dose levels, high doses in OARs can be reduced without compromising PTV homogeneity and conformity as much as with a large α value alone.

The optimal combination identified in this study was an α value of 3 or 5 for the parotids and 20 for the brainstem and spinal cord, which yielded substantial dose reductions, improved conformity and uniformity, faster optimization, and a modest MU increase. In contrast, α value combinations such as 10 and 15 or 10 and 20, although achieving the greatest D_{mean} reduction in the parotid glands, slightly compromised PTV dose distribution, with a modest increase in D_{max} to the spinal cord and brainstem, as well as elevated MU. These findings highlight the need for a careful balance of α values to optimize OAR sparing while preserving adequate PTV coverage. Figure 4 illustrates the dose uniformity and conformity achieved with optimal combinations such as 3 and 20, as well as 5 and 20. In comparison, combinations such as 5 and 15 as well

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as 10 and 20 resulted in the formation of hotspots and small segments, and reduced PTV coverage, further emphasizing the need for a balanced α value selection.

Another optimization parameter assessed in this study was the NTO settings. In DV plans, automatic NTO yielded in better PTV conformity and uniformity, although it provided less OAR sparing than manual NTO. This is because automatic NTO dynamically adjusts based on the proximity of the high-dose areas to the target, adapting to the patient's anatomy and optimization objectives during the planning process [8]. Consequently, in DV+gEUD plans, the performance of automatic NTO is affected by the presence of gEUD objectives, as its effectiveness depends on the overall optimization priorities and objectives applied.

In both DV and DV+gEUD plans, manual NTO settings with a lower dose fall-off of 0.15 provided a more uniform dose in PTV by allowing a gradual decrease outside PTV, but this occurred at the expense of conformity, as the dose spread to nearby OARs. On the other hand, a higher dose fall-off of 0.5 produced a sharper dose reduction outside the PTV, improving conformity but slightly reducing PTV dose uniformity. Therefore, manual NTO with a dose fall-off of 0.5 consistently yielded the lowest D_{max} and D_{mean} for most OARs, particularly in DV+gEUD plans with gEUD objectives in the brainstem and spinal cord. Figure 5 illustrates that, compared with automatic NTO, manual NTO results in isodose lines that conform more closely around PTV and exhibit a steeper dose fall-off outside the target.

Regarding MU and optimization time, automatic NTO resulted in the lowest MU values but the longest optimization times. In contrast, manual NTO with a dose fall-off of 0.5 produced the highest MU values and the fastest optimization times, with significant differences observed only for optimization time. The increase in MU values associated with manual NTO and the inclusion of gEUD objectives is likely due to the more complex MLC modulation required to improve PTV conformity and OAR sparing [21]. Overall, automatic NTO provided better PTV conformity and uniformity but less OAR sparing, whereas manual NTO with a dose fall-off of 0.5 achieved superior PTV conformity and OAR sparing at the cost of slightly reduced dose uniformity.

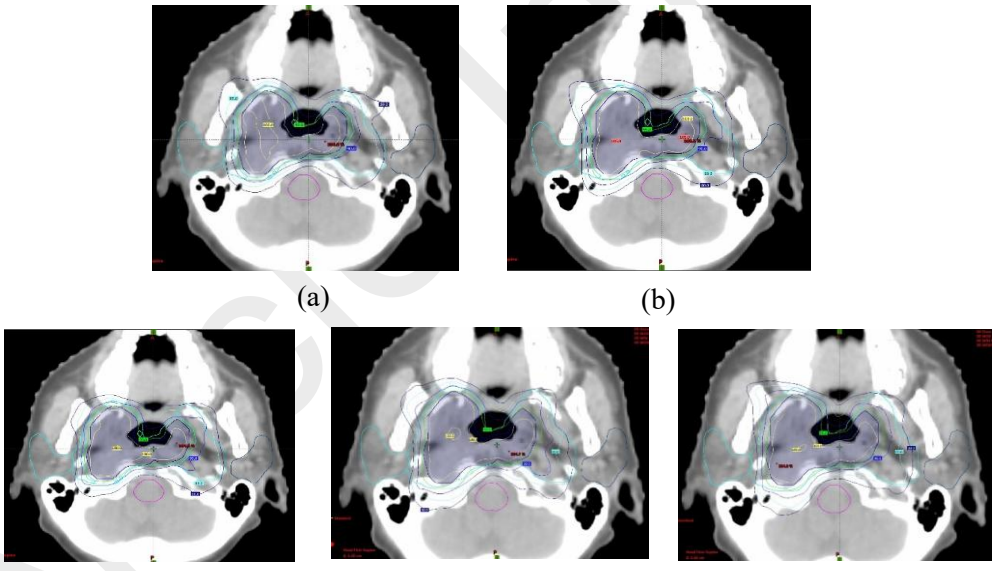


Fig. 4. Axial view of distribution isodose lines for the second patient, (a) DV plans, (b) DV+gEUD plan combination α value of 5 and 15, (c) 3 and 20, (d) 5 and 20, and (e) 10 and 20.

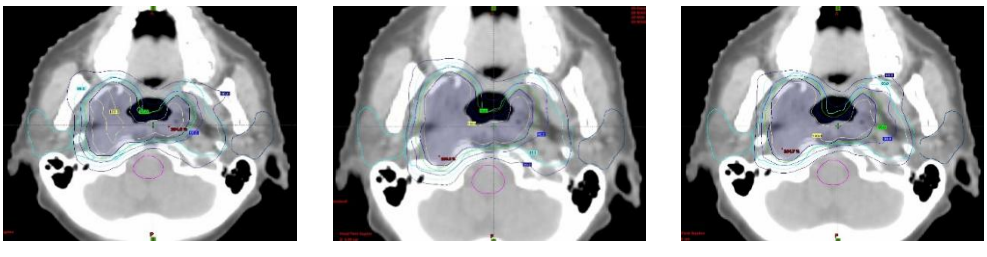


Fig. 5. Distribution of isodose lines for NTO settings (a) automatic NTO, (b) manual NTO dose fall-off of 0.15, and (c) manual NTO dose fall-off of 0.5.

These findings align with studies in brain and endometrial IMRT that reported significant results, but differ from those in prostate VMAT and lung SBRT [8-11]. Regardless of the NTO settings, DV+gEUD plans with α value combinations of 3 and 20, as well as 5 and 20, delivered optimal results.

In addition to optimization strategy selection, the applied dose constraints played an important role in shaping the observed dose distributions. In this study, relatively tight dose constraints were applied to critical serial organs, particularly the spinal cord and brainstem, compared to conventional QUANTEC recommendations. This approach was intentionally chosen to reflect clinically challenging NPC cases, in which these structures are often near or overlapping with the target volumes. The use of stricter constraints allowed evaluation of the robustness of DV and gEUD-based optimization strategies, as well as different NTO settings, under demanding planning conditions. Despite the tightened limits, acceptable PTV coverage, conformity, and dose uniformity were maintained, indicating that the proposed optimization approaches can effectively balance target coverage and OAR sparing. These findings suggest that tighter constraints may be clinically feasible in selected cases requiring conservative neurological protection, while routine clinical practice should continue to individualize constraint selection based on patient-specific anatomy and risk.

After evaluating the optimization parameters, we compared the outcomes generated by the AAA and AXB_{Dm} algorithms across all planning types. For all three PTVs, the AXB_{Dm} calculations generally yielded lower D98%, D95%, and D50% values than AAA, with an average difference of approximately 1.3%. However, D2% values showed greater variability, with statistically significant differences observed only at D95% for PTV 59.4 Gy. This discrepancy can be attributed to the anatomical complexity of NPC cases, in which the PTV is in regions comprising heterogeneous tissues, including bone, air, and soft tissues.

Previous studies have reported similar trends, indicating that AXB_{Dm} tends to estimate lower dose values than AAA for PTV involving soft tissues and bone, while yielding slightly higher dose values in air, with minimal differences overall [2]. Thus, our findings suggest that the lower D95% in the AXB_{Dm} for PTV 59.4 Gy is primarily related to its bone and soft tissue composition. In terms of evaluation indices, AXB_{Dm} generally performed less favorably than AAA across all planning types, with significant differences observed only in HI. This finding corresponds with the observed variations in dose estimation between the two algorithms.

For OARs, AXB_{Dm} consistently produced lower D_{max} and D_{mean} values than AAA across all planning types, with the most significant and largest dose reductions occurring in structures with high bone content due to their higher density and atomic number (Z). Among all structures, the lens exhibited the largest differences, likely because of its location in a low-density region. Variability in dose estimation was also observed for the optic nerve, optic chiasm, and trachea, indicating the impact of their proximity to complex anatomical regions involving air cavities and bone structures. While AXB_{Dm} provides improved OAR sparing, transitioning from AAA to AXB_{Dm} requires careful consideration of PTV coverage and MU evaluation, particularly due to its impact on lower dose regions.

Notably, in DV+gEUD plans, the combinations of α values of 3 and 20, as well as 5 and 20, the use of automatic NTO and manual NTO with a dose fall-off of 0.5, provided optimal results regardless of the dose calculation algorithm used. This indicates that AXB_{Dm} and the AAA produce comparable plan quality for these specific parameter variations, without a significant impact on overall plan performance.

Gamma index evaluation revealed that the addition of gEUD objectives to selected OARs alongside DV objectives did not increase planning complexity. However, the GPR values for 3%/2 mm criteria in both DV and DV+gEUD plans calculated using the AAA algorithm did not meet the 95% tolerance limit, whereas the plan calculated with the AXB_{Dm} algorithm satisfied this requirement. These results indicate that the choice of dose calculation algorithm significantly affects the GPR values.

AXB_{Dm} explicitly models radiation interaction in tissues with varying densities and atomic compositions, which is critical in NPC cases due to the presence of air-tissue and tissue-bone interfaces, as well as bone structures. In contrast, AAA assumes a water-like medium. Therefore, AXB_{Dm} provides more accurate dose predictions in heterogeneous regions, resulting in improved agreement between the measured and calculated dose distributions.

CONCLUSION

This study demonstrates that incorporating DV and gEUD objectives can improve OAR sparing while maintaining conformity and uniformity of PTV, without increasing planning complexity. The choice of NTO settings influences the trade-off between PTV uniformity and OAR sparing. Appropriate selection of optimization parameters plays an important role in achieving an optimal

balance between target dose quality and OAR protection. In addition, differences between dose calculation algorithms affect dose estimation, particularly in anatomically heterogeneous regions such as NPC, emphasizing the importance of algorithm selection during treatment planning. Overall, robust VMAT planning for NPC requires careful optimization strategy selection and algorithm evaluation. Further study with larger samples is needed to establish the tolerance levels for specific α values for different organs. Biological evaluation related to the use of gEUD is also warranted.

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AUTHOR CONTRIBUTION

Annissaa Ghaasyiyah and Akbar Azzi equally contributed as the main contributors of this paper. Aloysius Mario Yudi Putranto, Dewa Ngurah Yudhi Prasada, and Meirisa Ambalinggi contributed to data collection. Dwi Seno Kuncoro Sihono read and approved the final version of the paper.

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